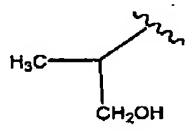
## REMARKS

Claims 1-20 and 24-29 are pending in the Application. Claims 3, 4, 9 and 13-16 are withdrawn as non-elected subject matter. Applicants preserve the right to pursue the withdrawn subject matter by way of divisional application(s) if Applicants choose to do so.

The allowance of Claim 18 is sincerely appreciated.

Claims 20 and 24-27 were rejected under 35 U.S.C. § 112, first paragraph, on enablement grounds. The Examiner stated that the specification "while enabling for a method of inhibiting CDK2 and/or a method of treatment of specific cancers (recited in claim 24), does not reasonably provide enablement for inhibiting all types of cyclin dependent kinases or for the treatment of all other diseases embraced by the instant claims." (Pages 5-6 of the Office Action). Applicants believe that the **Background of the Invention** provides sufficient enablement for linking CDK2 with other cyclin dependent kinases and the various diseases. However, in the interest of furthering the prosecution, Applicants have now cancelled claims 20-24 and amended claim 25 suitably. Applicants believe that this amendment should satisfy the Examiner's concerns. Applicants, however, would like to emphasize that the amendment is being done with a sincere desire to further the prosecution along and should not be perceived as an admission that the cancelled or given-up scope of the claims is not patentable. Applicants preserve the right to pursue such scope later by divisional application(s), if Applicants choose to do so.

Claims 8 and 24 were rejected under 35 U.S.C. § 112, first paragraph, on indefiniteness grounds. As stated above, Claim 24 is now cancelled. The moiety "2-ylpropanol" in claim 8 is precisely the way IUPAC nomenclature is for:




This moiety for $R^3$ is present in the compound in Claim 17 (No. 34 counting from the beginning of the list of compounds or No. 9 counting from the bottom of the list of compounds in claim 17; or page 7 of this Amendment, bottom

left). Thus, it is a well known way of naming that group. The other way to name this would be "propan-1-ol-2-yl". To overcome the objection, Applicants have now amended claim 8 with the name "propan-1-ol-2-yl". Applicants would like to stress that either way of naming should be appropriate.

Claims 1-2, 5-8, 10-12, 17,19-20 and 24-29 were rejected under 35 U.S.C. § 103(a) as being obvious over Burns *et al*, WO 02/060492. The '492 publication discloses certain pyrazines. In the Office Action of March 12, the Examiner pointed out that the reference compounds lack a substitution in the (present) $R^2$ position. However, the Examiner stated: "Since the instant compounds differ by having a methyl group in place of the hydrogen disclosed for reference compounds (i.e., differing by a $CH_2$ group), the instantly claimed compounds are homologs of the reference compound. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar utilities. ". In its response of March 31, 2004, Applicants filed two publication references (Exhibit A and Exhibit B in the Response of March 31, 2004) which, Applicants believed, clearly showed that even small changes in the groups on a compound can drastically and significantly change the biological activity that the prediction of the utilities becomes impossible. In the present Office Action, the Examiner has maintained the same rejection stating that "neither of the references (that Applicants submitted) showed structurally analogous compounds". Applicants would respectfully like to disagree with the Examiner's contention. The instantly claimed compounds are structurally dissimilar from the teaching of the '492 publication and the instant structures or synthesis are not taught by the '492 publication. Additionally, the fact that even small changes in the structure of a molecule, even a simple homolog change, can drastically, significantly and unpredictably change the biological activity is well known in the art. Applicants are enclosing three articles to illustrate this point. Applicants believe that these are "in analogous art".

1st illustration (EXHIBIT C): Applicants would like to bring to the attention of the Examiner the attached copy of J. Hunt *et al*, *J. Med. Chem.*, 47, 4054- 4059 (2004), with relevant data on page 4050 highlighted. This article compares the effect of changing H to methyl, among others, in the

structure of pyrrolotriazines on their kinase inhibitory activity. Thus, for example, compounds 13 and 16 in Table 1 in EXHIBIT C differ only as H versus methyl. As the article clearly shows, the activity *drops* from 0.51 nM for the H-containing compound to 29.4 nM for the methyl compound, which is a huge and significant drop.

2nd illustration (EXHIBIT D): Yet another evidence to the same effect is provided by G. Rewcastle *et al, J. Med. Chem.*, 41, 742-751 (1998). Here too, the effect of changing H to Me can be seen in the highlighted compounds 6b and 9b in Table 1 on page 744. When X is changed from H to Me, the kinase inhibitory activity ($IC_{50}$) goes *up* from 9 nM to 0.45 nM (the reverse to what EXHIBIT C shows), demonstrating the unpredictability of structural changes on biological activity.

3rd illustration (EXHIBIT E): Yet another evidence to the same effect is provided by Y-T Chang *et al, Chemistry & Biology*, 6(6), 361-375 (June 1999). Here too, the effect of changing H to Me to ethyl to Isopropyl to n-butyl to cyclopentyl can be seen in the highlighted compounds 1, 24, 12, 3, 2 and 21 respectively in Figure 9 on page 366. When R is changed from H to Me to ethyl to isopropyl to n-butyl to cyclopentyl, the CDK2/cyclic A activity ratio changes all over the place from about 7 (see the bar chart) to about 3.8, to about 0.5, to about 1, to about 2.4, to about 0.8 respectively, demonstrating the unpredictability of structural changes on biological activity.

Therefore, Applicants want to emphasize the lack of predictability or correlation between even minor structural changes (even homologs) and biological activity in a molecule. Such a change in activity can at times lead to lack of utility too in certain compounds. Thus, Applicants strongly and respectfully disagree with the statement that when two compounds differ "by having a methyl group in place of hydrogen .... (i.e., differing by a $-CH_3$ group), .... such structurally homologous compounds would be expected to possess similar utilities." The instant Office Action, Page 11, lines 10-15). Withdrawal of the 103(a) rejection is, therefore, respectfully requested.

There being no other rejections pending, Applicants believe that the claims, as amended, are in allowable condition and such an action is earnestly solicited. If the Examiner has any questions, the Examiner is invited to contact the undersigned.

5

September 16, 2004

Respectfully submitted,

Schering-Plough Corporation
2000 Galloping Hill Road
Patent Department, K-6-1,1990
Kenilworth, NJ 07033
Tel: (908) 298-5068
Fax: (908) 298-5388

Dr. Palaiyur S. Kalyanaraman
Attorney for Applicants
Reg. No. 34,634